

Utility of respiratory vaccination with recombinant subunit vaccines for protection against pneumonic plague.

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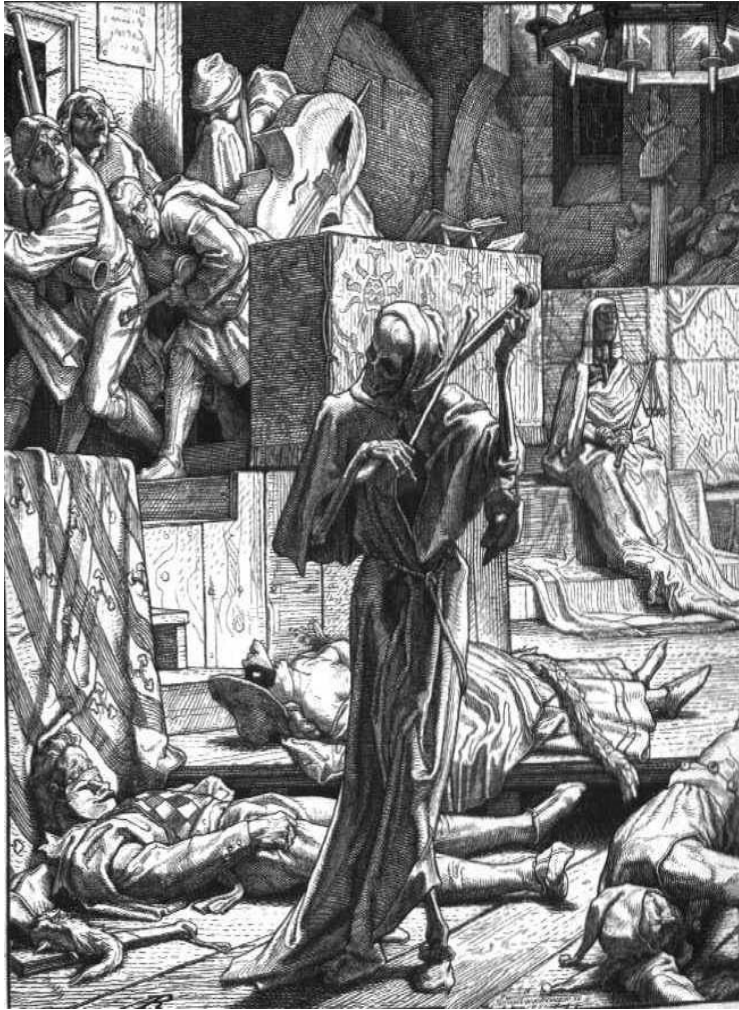
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Plague

Causative agent: *Yersinia pestis*

- a.k.a. “The Black Death”
- Endemic disease worldwide
- Normally infects rodents
- Three forms: bubonic, septicemic, and pneumonic plague
- Plague can be aerosol transmitted, has a rapid onset and high mortality (100%)



Respiratory vaccination:

Why vaccinate via the respiratory tract?

- Immunity at mucosal sites can prevent pathogen infection of the host.
 - A) oral poliovirus vaccine
 - B) inhaled influenza vaccine
 - C) kennel cough & Newcastle vaccines (pets & livestock)
- Inhaled vaccines could be easily administered in the field.

Plague vaccine:

Recombinant subunit vaccine for plague: a fusion protein that combines the F1 capsular protein and secreted V protein (F1-V). When given intramuscularly (i.m.) with alhydrogel, F1-V protects mice against a lethal pneumonic plague challenge.

Mucosal adjuvant: monophosphoryl lipid A (MPL), in an aqueous formulation (MPL-AF)



Respiratory Vaccination: Proof-of-Principle Experiments

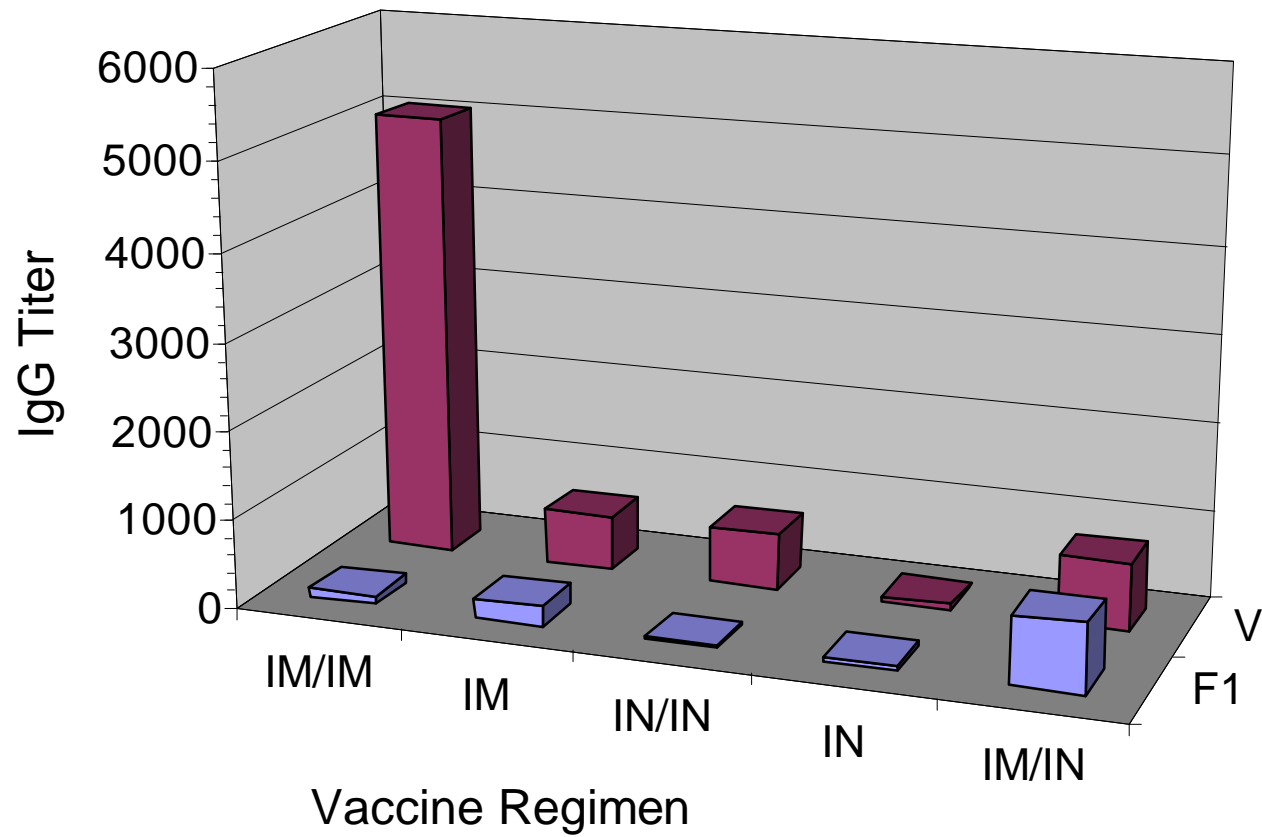
Species: *Mus musculus*, Swiss/Webster strain, adult, both sexes

Experiment outline:

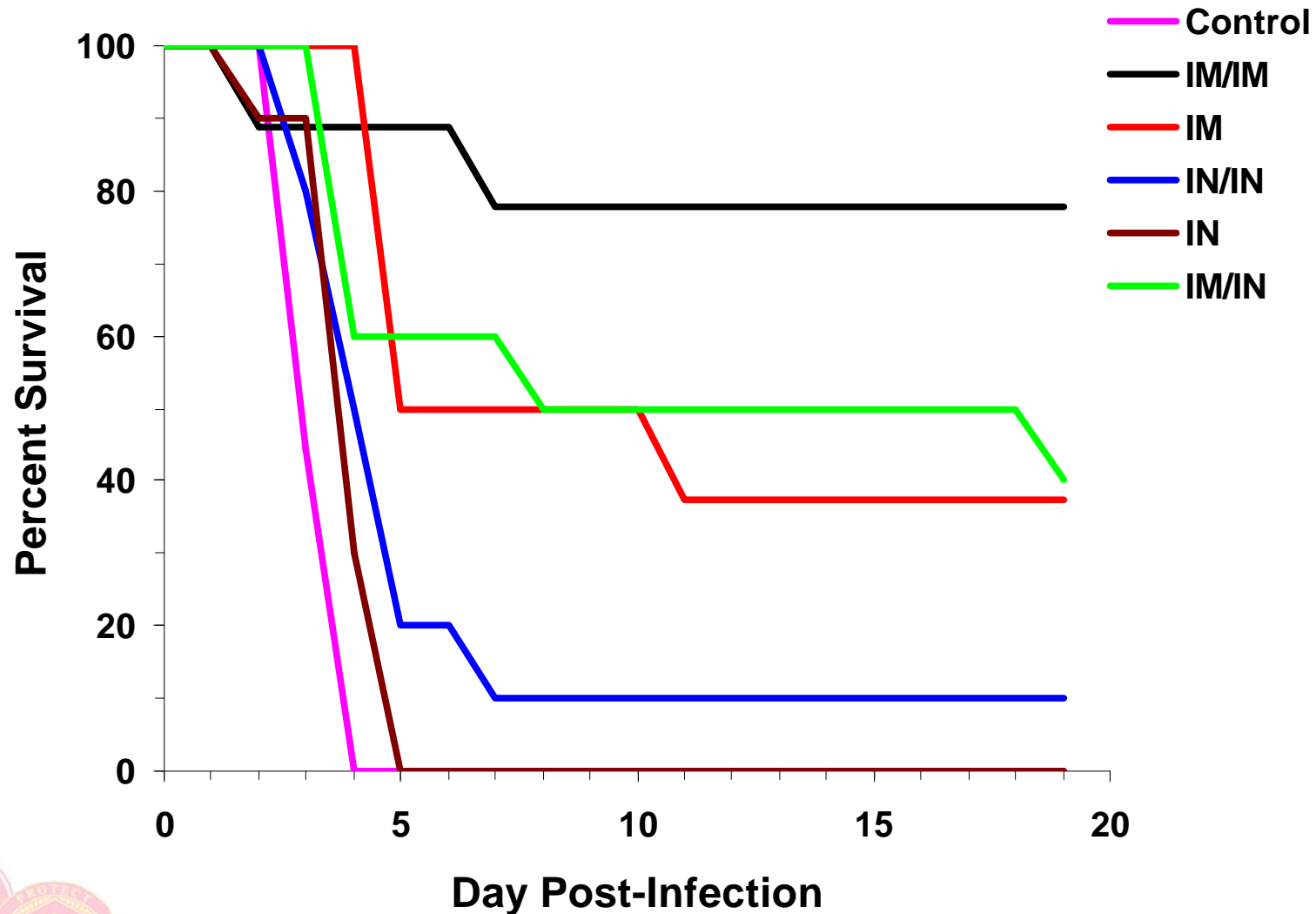
- One or two doses of vaccine, spaced 4 weeks apart
- Fourteen mice per group; four for BAL/sera collection
- 6 weeks after final vaccination - collect BAL/sera, challenge (100 LD₅₀ of aerosolized *Yersinia pestis* CO92)
- Monitor mice for 20 days after challenge
- BAL & sera measured for antibody titers against F1 & V using the fluorescent microsphere immunoassay (FMIA). FMIA allows for simultaneous measurement of antibody to F1 & V.



IgG titers against F1 and V in BAL of F1-V vaccinated mice.



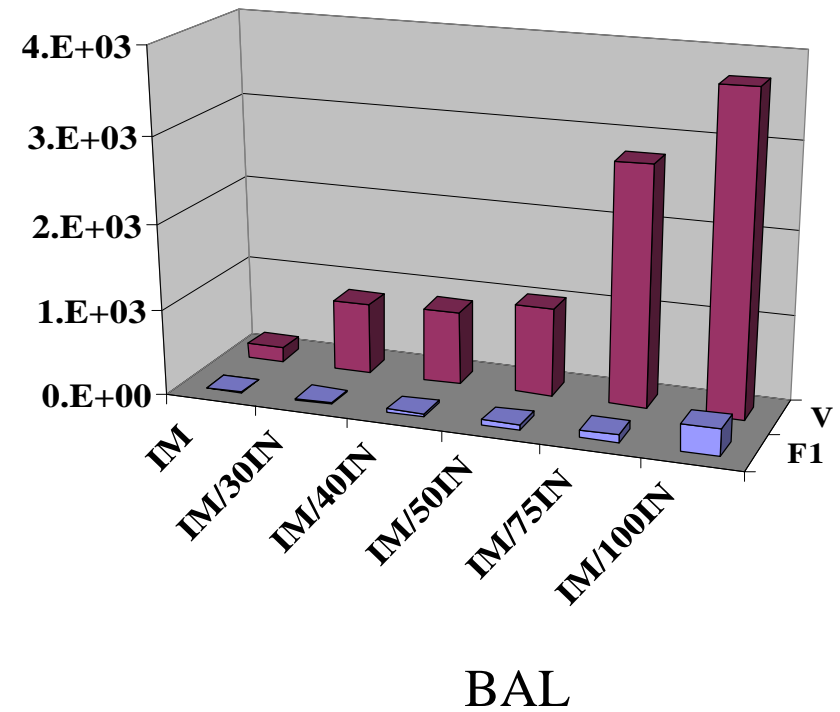
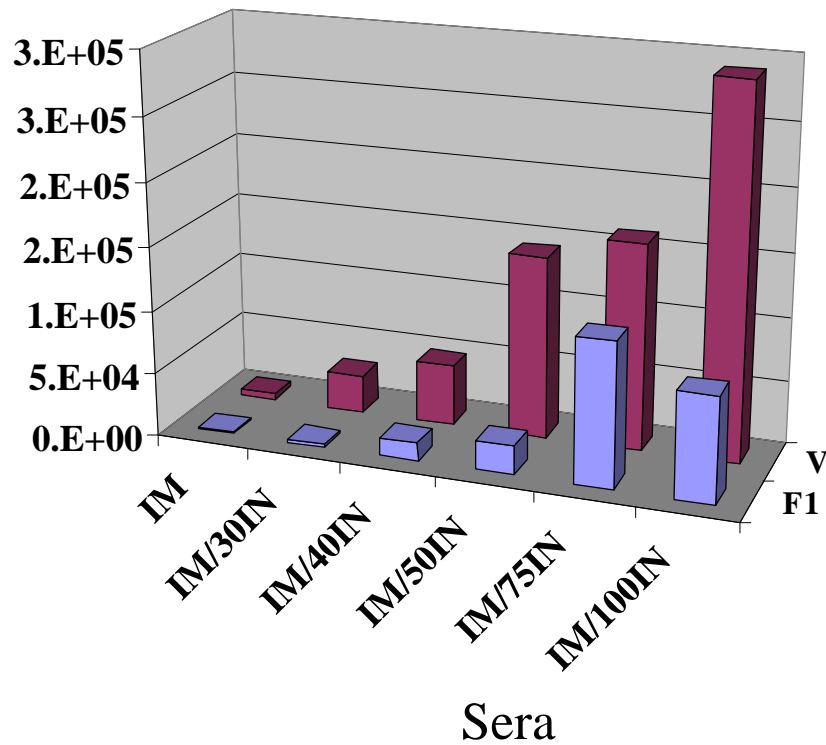
Intranasal vaccination fails to protect mice against aerosolized *Yersinia pestis*



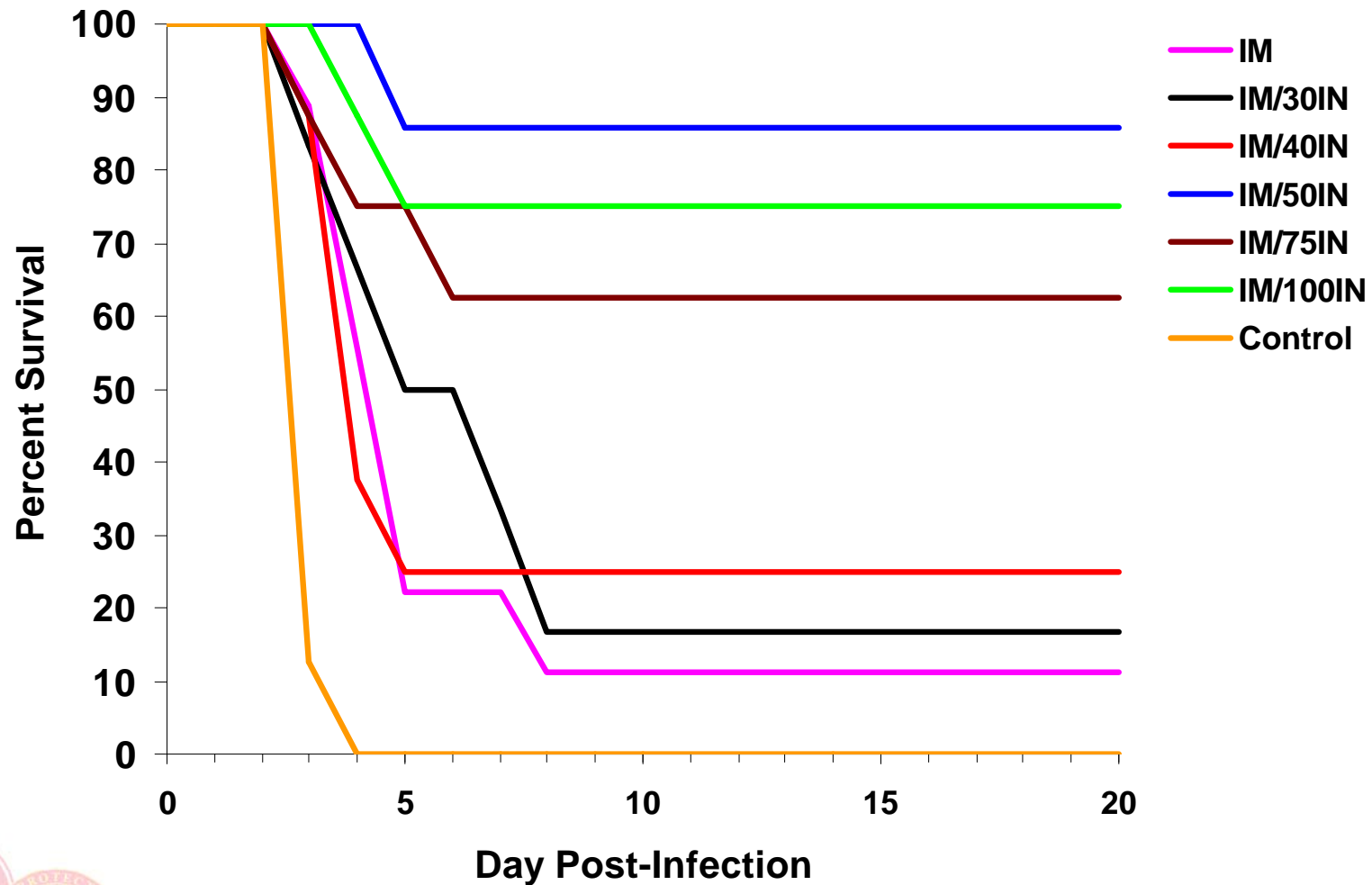
Challenge strain: *Yersinia pestis* CO92
Challenge dose: 100 LD₅₀



IgG titers after vaccination using intranasal F1-V as a booster.



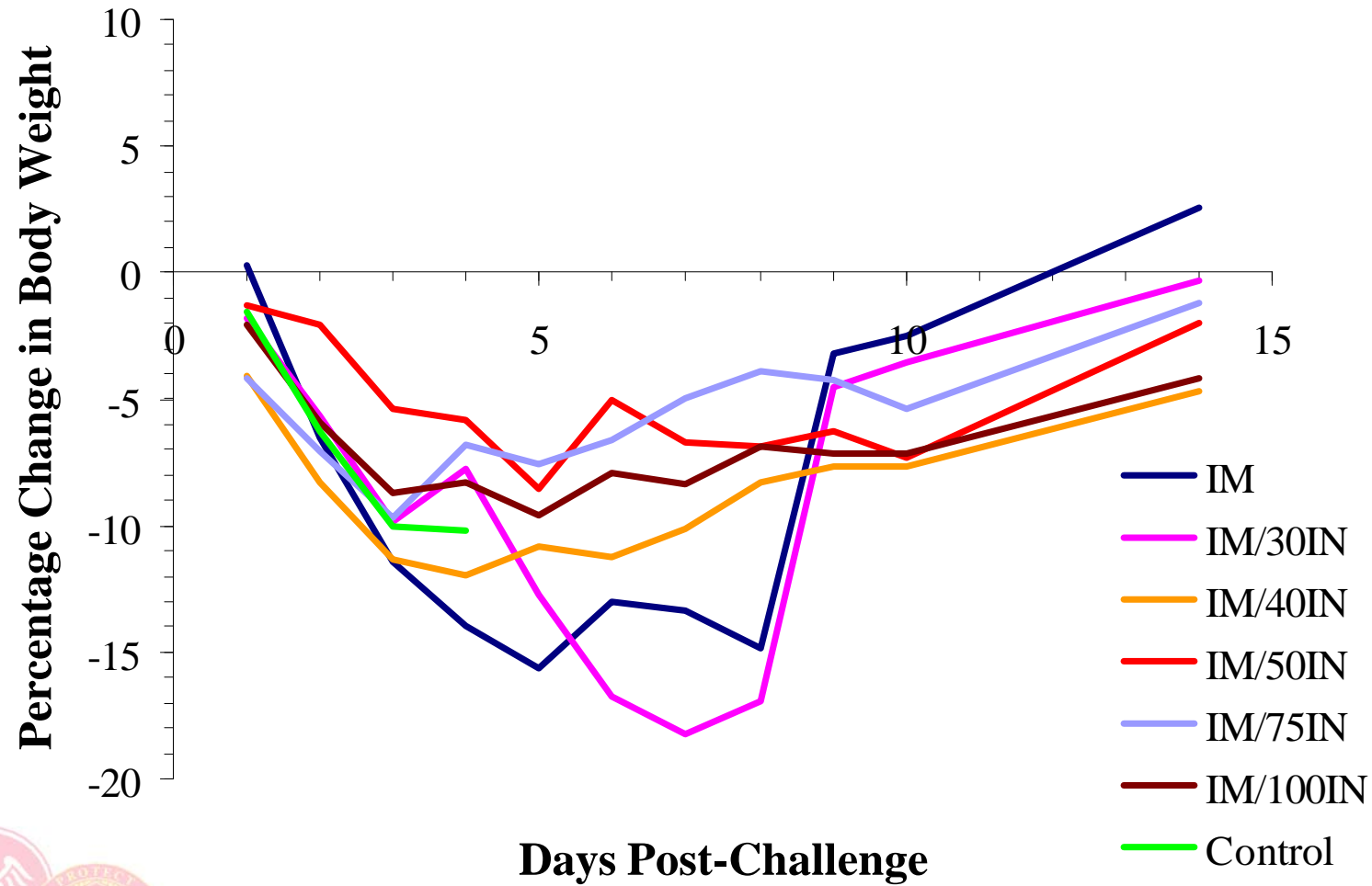
Intranasal vaccination elicits protective immunity when used as a booster.



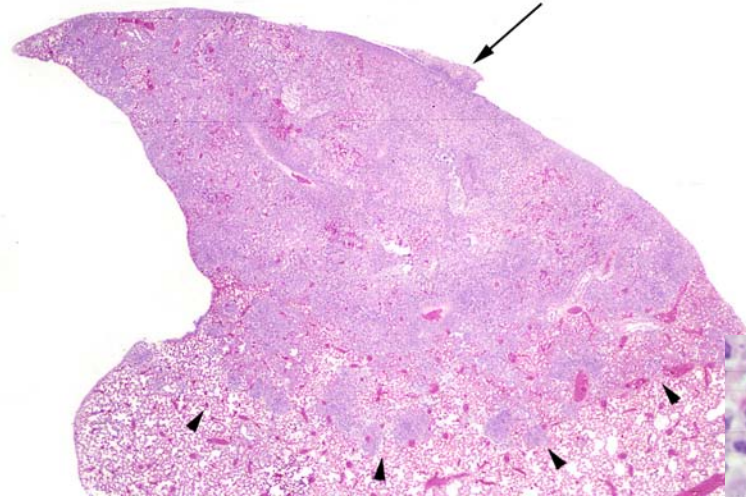
Challenge strain: *Yersinia pestis* CO92
Challenge dose: 100 LD₅₀



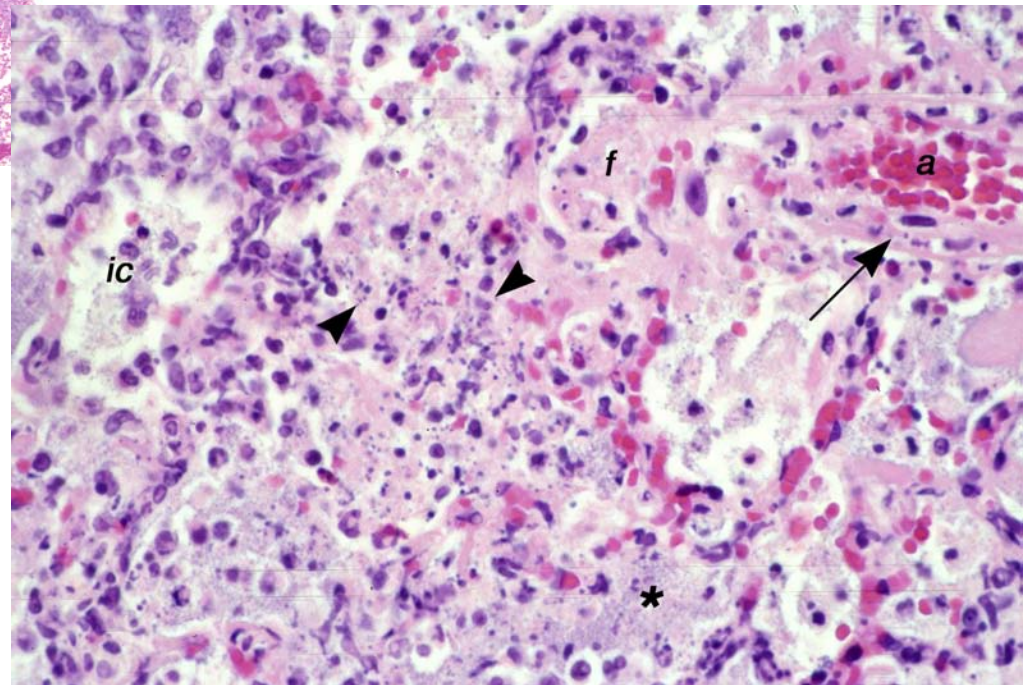
Percentage change in body weight after challenge.



Severe pneumonia in lungs of vaccinated mice that succumb to infection.



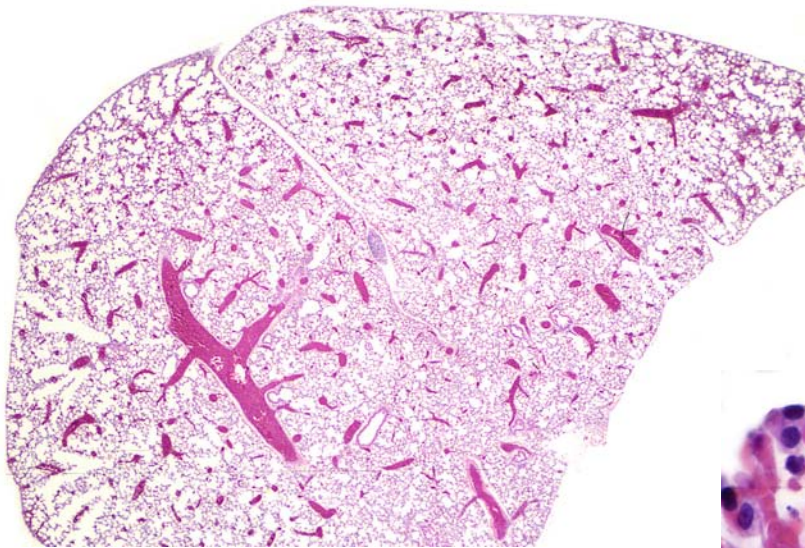
Original magnification, 20X.



Original Magnification, 600X.

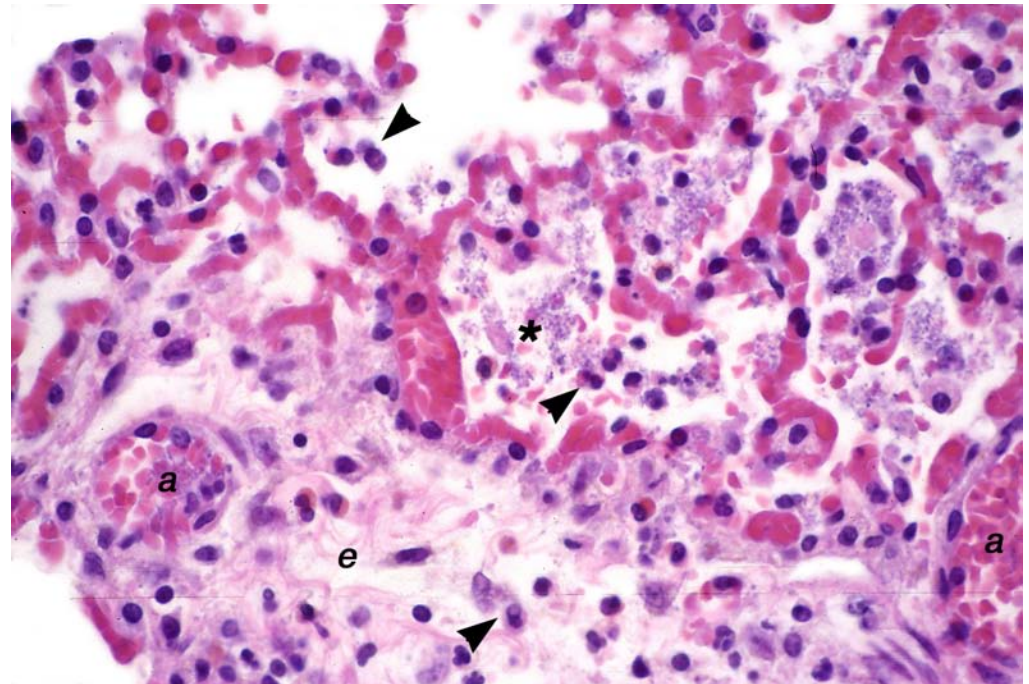


Lungs of control mice that succumb to infection are essentially clear.



Original magnification, 20X.

Original Magnification, 600X.



Conclusions:

- Intranasal vaccination alone failed to elicit a good immune response and did not protect mice against pneumonic plague challenge.
- Intranasal administration of F1-V + MPL-AF can serve as a booster to primary immunization with F1-V + alhydrogel injected i.m.. The levels of both systemic and mucosal immunity is determined by the dose of F1-V given as an intranasal boost.
- The data from the second experiment suggests that both systemic and respiratory immunity are necessary for protection against pneumonic plague. Systemic immunity prevents dissemination of *Yersinia pestis* while respiratory immunity prevents development of fatal pneumonia.

Future Plans:

- Vaccinate mice using aerosolized F1 with MPL-AF to target the lower respiratory tract.



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